multimers. Compositions containing factor VIII/vWF-complex as purified by cation exchange chromatography are also provided.--

REMARKS

I. Status of the Claims

Claims 17-37 are pending, with claims 26-37 withdrawn from consideration as drawn to a non-elected invention. Thus, claims 17-25 are currently under examination. Upon entry of this amendment, claims 17-21 and 25 are amended without prejudice or disclaimer.

None of the amendments are made for reasons of patentability. Instead, the claims are amended to correct typographical errors, to reword the claims to a more succinct form and/or to more distinctly describe the claimed invention. New claims 38 and 39 and the amendment to claims 17, 21 and 25 are supported, for example, at the following sections of the specification:

Claim 17: Paragraph bridging page 4 and 5; and paragraph bridging page 5 and 6.

Claim 21: Page 13, lines 1-5.

Claim 25: Page 10, lines 1-3.

Claim 38 and 39: Page 5, line 18 to page 6, line 1; and paragraph bridging pages 7 and 8.

II. Objections to the Specification

The specification has been amended to include section headings and to be ordered as requested by the Examiner. These amendments introduce no new matter.

III. Abstract

Applicants direct the Examiner's attention to page 33 of the application as filed which includes an abstract. Nonetheless, in case this page has been misplaced or is otherwise not available, Applicants have provided a new abstract as requested by the Examiner. This amendment introduces no new matter.

IV. Information Disclosure Statement

The Examiner contends that the Information Disclosure statement filed May 8, 2000 fails to comply with the provisions of the MPEP because it includes documents that have not been

translated. In response, Applicants direct the Examiner's attention to the supplemental information disclosure statement filed August 9, 2001, which the Examiner has considered. As indicated in the transmittal letter, this statement includes English language equivalents for those documents cited in the May 8, 2000 statement that were not in English.

Specifically, the English language equivalents are as follows:

Ref. No.	Document No.	English Language Equivalent
AB	WO 93/15199	5,876,969
AC	WO 96/10584	5,877,152
AD	WO 97/34930	6,228,613
AE	WO 97/39033	CA 2,251,558
AF	WO 98/38219	AU 737986
AI	EP 0 416 983	5,679,776
AK	EP 0 714 987	5,858,658
AL	EP 0 714 988	5,789,153
AM	DE 35 04- 385	4,578,218

English language equivalents of documents AF (Australian Patent No. 737986) and AN and AO are enclosed herewith.

V. Non-Statutory Double Patenting

As this rejection is a provisional double patenting rejection, Applicants request that this rejection be held in abeyance until notification of allowable subject matter.

VI. Rejection of Claims under 35 U.S.C. §112

Claims 17 and its dependent claims are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for the use of the phrase "particularly containing". The claim has been amended to delete the word "particularly" as requested by the Examiner, thus mooting this ground of rejection. Claim 17 has also been amended to define the acronym for factor VIII/vWF-complex as requested by the Examiner.

Claim 21 is also said to be indefinite for use of the phrase "particularly free." This claim has been amended to delete the word "particularly," thus overcoming the rejection.

VII. Rejection of Claims under 35 U.S.C. §102

Claims 17-25 stand rejected under 34 U.S.C. §102(b) as allegedly anticipated by European Patent Application 600 480 to Arrighi et al. ("Arrighi"). For the reasons that follow, Applicants respectfully disagree.

A. Currently Claimed Method

The present claims are directed to a method for purifying a factor VIII/vWF-complex that contains high molecular weight multimers using cation exchange chromatography. Claim 17 has been amended to state more specifically that this is achieved by eluting factor VIII/vWF-complex from a cation exchanger by a step-wise elution process to recover a solution containing factor VIII/vWF-complex that contains high molecular weight vWF multimers. Thus, according to the currently claimed methods, factor VIII/vWF-complex itself is eluted from the cation exchange column in a step-wise fashion. Claim 18 more specifically states that this step-wise elution initially involves eluting factor VIII/vWF-complex containing low molecular weight vWF multimers, as well as factor VIII free from platelet agglutinating vWF activity and factor VIII:C, at a salt concentration of between ≥250 mM and ≤300 mM. As recited in claims 19 and 20, factor VIII/vWF-complex containing high molecular weight vWF multimers is subsequently eluted at a salt concentration of ≥300 mM (claim 19) or ≥350 mM (claim 20) .

B. Arrighi Distinguished

Arrighi describes a very complex process for purifying factor VIII/vWF-complex that begins with an anion exchange purification step, followed by treatment with aluminum hydroxide, removal of precipitated proteins by centrifugation, clarification of the factor VIII/vWF-complex by filtration through clarification filters, concentration and diafiltration of the factor VIII/vWF solution, viral inactivation and then concludes with a cation exchange chromatography purification step.

The cation exchange purification step discussed by Arrighi, however, differs from the currently claimed methods in that it does not involve a process in which factor VIII/vWF-complex itself is eluted by a step-wise elution process from the cation exchanger. Instead Arrighi discusses a cation exchange process in which non-absorbed or weakly bound proteins (there is no indication in Arrighi that this includes any form of a factor VIII/vWF-complex) are eluted with a TC buffer (see, col. 4, lines 15-17; and col. 3, lines 4-7) in a first step. In a second step, "[t]he FVIII:C-FvW complex" is eluted with TE buffer (see, col. 4, lines 17-20). Hence, in the purification scheme discussed by Arrighi, factor VIII-vWF-complex is eluted from the cation exchanger in a single step, rather than in a step-wise fashion. This difference by itself clearly distinguishes the currently claimed methods from those discussed by Arrighi.

Certain embodiments of the currently claimed invention such as recited in claim 18 are further distinguished in that the factor VIII/vWF-complex containing low molecular weight vWF multimers and certain other contaminating proteins is eluted at a salt concentration of $\geq$250 mM and $\leq$300 mM. Arrighi does not discuss such a step. The TC buffer utilized to elute non-absorbed or weakly bound proteins contains 130 –170 mM sodium chloride and 1-3 mM calcium chloride, making the maximum salt concentration 173 mM (170 mM sodium chloride plus 3 mM calcium chloride = 173 mM). This salt concentration is less than the minimal salt concentration ($\geq$250 mM) recited in claim 18 and those claims that depend upon it (e.g., new claims 38 and 39). And there is no indication in Arrighi that the TC buffer is effective to elute factor VIII/vWF complexes that contain low molecular weight vWF multimers. Claims 18, 38 and 39 are thus further distinguished from the methods discussed in Arrighi for this reason.

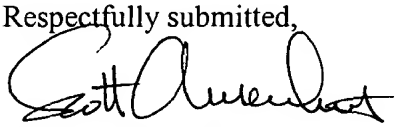
While the method discussed by Arrighi are clearly different than the currently claimed invention, Arrighi also fails to suggest the present invention. A major difficulty in the purification of a complex such as the factor VIII/vWF-complex is to identify appropriate elution conditions that prevent the components of the complex (which are not covalently bound but associated by electrostatic forces) from disassociating from one another (e.g., factor VIII disassociating from vWF). The difficulty is further compounded in the presently claimed invention in that the goal is to obtain factor VIII/vWF-complex which contains high molecular

weight vWF multimers. This means that elution conditions must also be chosen such that high molecular weight vWF multimers rather than low molecular weight vWF multimers are obtained. There is no discussion in Arrighi regarding any of these issues whatsoever.

For all the foregoing reasons, it is submitted that Arrighi fails to teach or suggest each and every element of the currently claimed invention. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The following section headings and text have been added before the first paragraph of the application:

CROSS-REFERENCES TO RELATED APPLICATION

This application is the U.S. national phase of PCT/AT98/00043, filed February 27, 1998, which claims priority to Austrian Application A 338/97, filed February 28, 1997.

FIELD OF THE INVENTION

The following text has been added before the second paragraph on page 1:

BACKGROUND

The following text has been added after the first paragraph on page 4:

SUMMARY

The following text has been added after the third paragraph on page 4:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification with cation exchanger;

Fig. 2 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification by means of a combined anion/cation exchange chromatography.

DETAILED DESCRIPTION

The first full paragraph on page 17 has been amended as follows:

The invention will now be explained in more detail by way of the following examples; ~~and the drawing figures,~~ however, it shall not be restricted to these exemplary embodiments.

The second and third full paragraphs on page 17 have been deleted:

~~Fig. 1 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification with cation exchanger;~~

~~Fig. 2 shows a vWF multimer analysis of factor VIII/vWF-complex from cryoprecipitate, before and after purification by means of a combined anion/cation exchange chromatography.~~

IN THE CLAIMS:

Claim 17 has been amended as follows:

17. (Once amended) A method of recovering factor VIII/von Willebrand factor-complex (factor VIII/vWF-complex) comprising:

(a)- providing a factor VIII/vWF-complex containing protein solution,

(b)- providing a cation exchanger,

(c)- binding said factor VIII/vWF-complex of said protein solution on said cation exchanger, and

(d)- ~~subjecting~~ eluting factor VIII/vWF-complex from said cation exchanger ~~to~~ by a step-wise elution ~~so as~~ process to recover factor VIII/vWF-complex ~~particularly~~ containing high-molecular weight vWF multimers ~~from said cation exchanger~~.

Claim 18 has been amended as follows:

18. (Once amended) A method as set forth in claim 17, wherein said factor VIII/vWF-complex is bound to said cation exchanger at a salt concentration of ≤250 mM and factor VIII/vWF-complex containing low-molecular weight vWF multimers, factor VIII free from platelet agglutinating vWF activity, and factor VIII:C is eluted and recovered at a salt concentration of between ≥250 mM and ≤300 mM.

Claim 19 has been amended as follows:

19. (Once amended) A method as set forth in claim 17, wherein said eluting step comprises eluting said factor VIII/vWF-complex ~~particularly~~ containing high-molecular weight vWF multimers ~~is recovered by step-wise fractionation~~ at a salt concentration of ≥300 mM.

Claim 20 has been amended as follows:

20. (Once amended) A method as set forth in claim 17, wherein said eluting step comprises eluting said factor VIII/vWF-complex ~~particularly~~ containing high-molecular weight vWF multimers ~~is recovered by step-wise fractionation~~ at a salt concentration of ≥350 mM.

Claim 21 has been amended as follows:

21. (Once amended) A method as set forth in claim 19, wherein said recovered factor VIII/vWF-complex ~~recovered~~ is a factor VIII/vWF complex-containing fraction ~~particularly~~ free from low-molecular vWF multimers, vWF degradation products, non complexed factor VIII ~~and factor VIII weakly bound to vWF~~, and is substantially free of contaminating nucleic acids.

Claim 25 has been amended as follows:

25. (Once amended) A method as set forth in claim 17, wherein said factor VIII/vWF-complex-containing protein solution is selected from the group consisting of a plasma, a plasma fraction, a cryoprecipitate, a cell-free supernatant of a recombinant cell culture, an extract of a recombinant cell culture, and ~~an enriched~~ a protein fraction enriched in factor VIII/vWF-complex.

IN THE ABSTRACT:

The following new paragraph has been added as the abstract at the end of the application:

ABSTRACT

Methods for recovering factor VIII/vWF-complex that involve binding factor VIII/vWF-complex from a protein solution to a cation exchanger and recovering factor VIII/vWF-complex by step-wise elution are disclosed. The recovered complex contains high-molecular vWF

multimers. Compositions containing factor VIII/vWF-complex as purified by cation exchange chromatography are also provided.